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=> s l2
L3          39 L2

=> d l3 1-20 ibib abs
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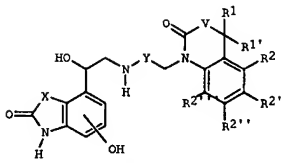
L3 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:11789 CAPLUS
DOCUMENT NUMBER: 146:121989
TITLE: Preparation of 1,4-dihydro-2H-3,1-benzoxazin-2-ones and related compounds for the treatment of respiratory diseases
INVENTOR(S): Konetzki, Ingo; Bouyssou, Thierry; Pestel, Sabine; Schnapp, Andreas
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
SOURCE: Ger. Offen., 74pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102005030733	A1	20070104	DE 2005-102005030733	20050701
US 2007037781	A1	20070215	US 2006-424558	20060616
WO 2007003554	A1	20070111	WO 2006-EP63650	20060628

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: DE 2005-102005030733A 20050701
OTHER SOURCE(S): MARPAT 146:121989
GI

L3 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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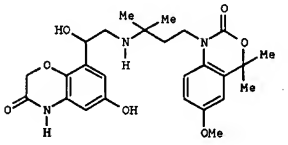

II

AB Title compds. I [Y = CRaRb(CH2)n; V = CH2, NH, O; X = O, NH, CH2O, etc.; Ra, Rb = H, alkyl, haloalkyl; R1, R1' = H, alkyl, cycloalkyl, etc.; R2, R2', R2'', R2''' = H, alkyl, OH, etc.; n = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, dihydrobenzoxazinone II was prepared from 2-amino-5-methoxyacetophenone in 5-steps. Of note is the combination of compds. I with long-acting beta-2-agonists for treatment of respiratory diseases.

L3 ANSWER 2 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1339527 CAPLUS
DOCUMENT NUMBER: 146:87582
TITLE: MRP4 inhibitors for the treatment of respiratory diseases
INVENTOR(S): Goeggel, Rolf; Cui, Yunhai
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma Gmbh & Co. KG
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006134022	A1	20061221	WO 2006-EP62690	20060530

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006286041	A1	20061221	US 2006-424596	20060616

PRIORITY APPLN. INFO.: EP 2005-105363 A 20050617
OTHER SOURCE(S): MARPAT 146:87582
AB The present invention relates to the use of MRP4 inhibitors for the treatment of respiratory diseases, pharmaceutical compns. containing them and processes for the preparation thereof.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1256669 CAPLUS
DOCUMENT NUMBER: 146:20293
TITLE: Novel medicament combinations for the treatment of respiratory diseases
INVENTOR(S): Pieper, Michael P.; Schnapp, Andreas; Nickolaus, Peter
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: U.S. Pat. Appl. Publ., 33pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006270667	A1	20061130	US 2006-420872	20060530
WO 2006128847	A2	20061207	WO 2006-EP62683	20060529

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: EP 2005-104702 A 20050531
OTHER SOURCE(S): MARPAT 146:20293
AB The present invention relates to new medicament combinations which contain in addition to one or more, preferably one, betamimetic, at least one anticholinergic and at least one PDE-IV inhibitor processes for preparing them and their use as pharmaceutical compns.

L3 ANSWER 4 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1090228 CAPLUS
DOCUMENT NUMBER: 146:54693
TITLE: Bridging Chemical and Biological Space: "Target Fishing" Using 2D and 3D Molecular Descriptors
AUTHOR(S): Nettles, James H.; Jenkins, Jeremy L.; Bender, Andreas; Deng, Zhan; Davies, John W.; Glick, Meir
CORPORATE SOURCE: Lead Discovery Informatics, Lead Discovery Center, Novartis Institutes for BioMedical Research Inc., Cambridge, MA, 02139, USA
SOURCE: Journal of Medicinal Chemistry (2006), 49(23), 6802-6810
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bridging chemical and biol. space is the key to drug discovery and development. Typically, cheminformatics methods operate under the assumption that similar chems. have similar biol. activity. Ideally then, one could predict a drug's biol. function(s) given only its chemical structure by similarity searching in libraries of compds. with known activities. In practice, effectively choosing a similarity metric is case dependent. This work compares both 2D and 3D chemical descriptors as tools for predicting the biol. targets of ligand probes, on the basis of their similarity to reference mols. in a 46 000 compound, biol. annotated chemical database. Overall, we found that the 2D methods employed here outperform the 3D (88% vs 67% success) in correct target prediction. However, the 3D descriptors proved superior in cases of probes with low structural similarity to other compds. in the database (singletons). Addnl., the 3D method (FEPOPS) shows promise for providing pharmacophoric alignment of the small mols.' chemical features consistent with those seen in exptl. ligand/ receptor complexes. These results suggest that querying annotated chemical databases with a systematic combination of both 2D and 3D descriptors will prove more effective than employing single methods.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:768981 CAPLUS
DOCUMENT NUMBER: 145:188711
TITLE: Preparation of phenoxyphenylpyrrolidones for treatment of HIV infection.
INVENTOR(S): Wu, Baogen; Nguyen, Truc N.; Ellis, David A.; He, Xiaohui; Anaclerio, Beth M.; Yang, Kunyong; Choi, Ha-Soon; Wang, Zhicheng; Marsilje, Thomas; He, Yun
PATENT ASSIGNEE(S): IRM LLC, Bermuda
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006081554	A2	20060803	WO 2006-US3217	20060130
WO 2006081554	A3	20061214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-648027P P 20050128
OTHER SOURCE(S): MARPAT 145:188711
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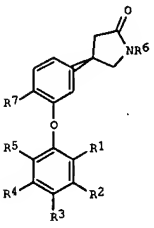

I

AB Title compds. [I; R1, R5 = H, cyano, halo, (substituted) alkyl, alkenyl, OR8; R8 = (substituted) alkyl, haloalkyl; R2, R4 = H, halo, cyano, (substituted) alkyl; R3 = H, cyano, alkyl; R6 = fused Ph heterocyclyl,

L3 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

pyridine N-oxide, pyridyl, pyridone, (substituted) Ph; R7 = halo, alkyl, alkenyl, alkynyl], were prepd. as inhibitors of HIV in cells (no data). Thus, 3-amino-5-[4-[4-chloro-3-(2-chloro-6-cyanophenoxy)phenyl]-2-oxopyrrolidin-1-yl]indazole-1-carboxamide was prepd. in many steps.

L3 ANSWER 6 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:499083 CAPLUS
DOCUMENT NUMBER: 145:167034
TITLE: Synthesis and evaluation of N-aryl pyrrolidinones as novel anti-HIV-1 agents. Part 1
AUTHOR(S): Wu, Baogen; Kuhen, Kelli; Ngoc Nguyen, Truc; Ellis, David; Anaclerio, Beth; He, Xiaohui; Yang, Kunyong; Karanewsky, Donald; Yin, Hong; Wolff, Karen; Bieza, Kimberly; Caldwell, Jeremy; He, Yun
CORPORATE SOURCE: Genomics Institute of the Novartis Research Foundation (GNF), San Diego, CA, 92121, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(13), 3430-3433
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:167034

AB The synthesis and preliminary structure-activity relationship of a series of pyrrolidinones are described. These pyrrolidinones have been characterized as novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) which are highly potent against wild-type and drug-resistant human immunodeficiency viruses (HIV-1).

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:381237 CAPLUS
DOCUMENT NUMBER: 144:432794
TITLE: Preparation of 4-(substituted-phenyl)-2-pyrrolidinone derivatives as selective phosphodiesterase 4 inhibitors
INVENTOR(S): Hopper, Allen T.; Dunn, Robert Francis; Kuester, Erik, Mikal; Conticello, Richard Dennis; Liu, Ruiping; Tehim, Ashok
PATENT ASSIGNEE(S): Memory Pharmaceuticals Corporation, USA
SOURCE: PCT Int. Appl., 199 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006044955	A1	20060427	WO 2005-US37568	20051020
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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US 2006135535	A1	20060622	US 2005-253812	20051020
PRIORITY APPLN. INFO.:			US 2004-619964P P	20041020
OTHER SOURCE(S):	MARPAT 144:432794			

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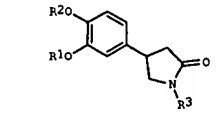

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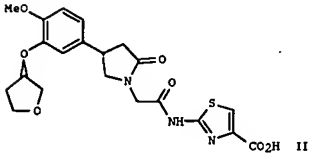

II

L3 ANSWER 7 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

AB Title pyrrolidinones compds. I [R1 = alkyl, wherein optionally 1 or more CH2CH2 groups are replaced by CH:CH or C.tplbond.C, (un)substituted cycloalkyl, aryl, arylalkyl, aryl-alkenyl, (un)saturated heterocyclyl, heterocyclyl-alkyl, etc.; R2 = (un)substituted alkyl; R3 = C(:O)R4; CH2CO2R5, (CH2)nSR5, etc.; R4 = (un)substituted alkoxyalkyl, cycloalkyl, aryl, arylalkyl, etc.; R5 = H, (un)substituted alkoxy/alkyl, cycloalkyl, aryl, etc.], were prepared The invention compds. exhibited improved phosphodiesterase 4 (PDE4) inhibition as compared to compds. such as rolipram and showed selectivity with regard to inhibition of other classes of PDEs. Selected I blocked the human PDE4 mediated conversion of cAMP to adenosine with IC50 values < 10 nM. Thus, I and their pharmaceutical compns. are useful for enhancing cognition and treating psychosis, allergic conditions, or inflammatory disease (no data). Thus, (4S)-1-[N-(4-ethoxycarbonyl-thiazol-2-yl)aminocarbonylmethyl]-4-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-2-pyrrolidone was prepared and tested in vitro and in rats as phosphodiesterase 4 inhibitor.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:149262 CAPLUS
DOCUMENT NUMBER: 144:239931
TITLE: Pharmaceutical compositions for the treatment of respiratory and gastrointestinal disorders
INVENTOR(S): Jung, Birgit; Himmelsbach, Frank
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma Gmbh & Co. KG
SOURCE: PCT Int. Appl., 321 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006015775	A2	20060216	WO 2005-EP8385	20050803
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006035893	A1	20060216	US 2005-189643	20050726
CA 2575541	A1	20060216	CA 2005-2575541	20050803
PRIORITY APPLN. INFO.:			EP 2004-18808 A	20040807
			WO 2005-EP8385 W	20050803
OTHER SOURCE(S):	MARPAT 144:239931			

AB The present invention relates to novel pharmaceutical compns. comprising at least 1 EGFR kinase inhibitor and at least one addnl. active compound selected from β-2 mimetics, steroids, PDE-IV inhibitors, p38 MAP kinase inhibitors, NK1 antagonists and endothelin-antagonists, processes for preparing the compns. and the use thereof as drugs in the treatment of respiratory or gastrointestinal complaints, as well as inflammatory diseases of the joints, the skin or the eyes. Thus, an inhalable powder contained an EGFR kinase inhibitor 150, formoterol fumarate dihydrate 50, and lactose 12,300 mg/capsule.

L3 ANSWER 9 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:46803 CAPLUS
DOCUMENT NUMBER: 144:135233
TITLE: Pharmaceuticals for inhalation comprising PDE IV inhibitors and glycopyrrolate salts
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Gm.b.H. & Co. K.-G., Germany
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1616567	A1	20060118	EP 2004-16878	20040716
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CA 2570433	A1	20060126	CA 2005-2570433	20050613
WO 2006008213	A1	20060126	WO 2005-EP52704	20050613
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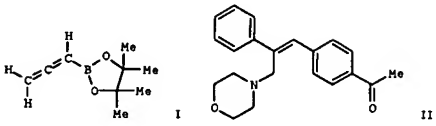
PRIORITY APPLN. INFO.:			EP 2004-16878 A	20040716
			WO 2005-EP52704 W	20050613

AB The present invention relates to novel pharmaceutical compns. based on PDE IV inhibitors and salts of glycopyrrolate salts, processes for preparing them and their use in the treatment of respiratory complaints. Thus, a formulation contained a glycopyrrolate salt 60, AWD 12281 200, lactose 12240 μg/capsule.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:38989 CAPLUS
DOCUMENT NUMBER: 144:273891
TITLE: Catalytic Four-Component Assembly Based on Allenylboronate Platform: New Access to Privileged Allylic Amine Structures
AUTHOR(S): Tonogaki, Keisuke; Itami, Kenichiro; Yoshida, Jun-Ichi
CORPORATE SOURCE: Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, 615-8510, Japan
SOURCE: Journal of the American Chemical Society (2006), 128(5), 1464-1465
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:273891
GI



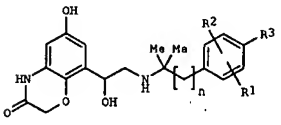
I II

AB A novel Pd-catalyzed four-component assembly based on allenylboronate platform was developed by which privileged allylic amine structures can be constructed in a regioselective, stereoselective, and diversity-oriented manner. The boryl group acts not only as a useful group that can be transformed to various functional groups afterward but also as a stereochem. controller in the generation of key (π-allyl)palladium intermediates. Thus, reaction of the allenylboronate pinacol ester I with PhI and morpholine in toluene containing EtN(CHMe2)2, Pd2(dba)3, and tris(2-furanyl)phosphine at 80° for 24 h gave a cis aminoalkenyl boronate intermediate which reacted with 4-IC6H4COMe in toluene/H2O containing Cs2CO3 at 90° for 24 h to give 73% (Z)-morpholinodiphenylethene II. A short synthesis of rolipram (selective phosphodiesterase-4 inhibitor) was demonstrated.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1155523 CAPLUS
DOCUMENT NUMBER: 143:416252
TITLE: Novel medicament combinations for the treatment of respiratory diseases
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: U.S. Pat. Appl. Publ., 50 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005239778	A1	20051027	US 2005-109094	20050419
DE 102004019540	A1	20051110	DE 2004-102004019540	20040422
DE 102004052987	A1	20060504	DE 2004-102004052987	20041103
AU 2005235419	A1	20051103	AU 2005-235419	20050418
CA 2559699	A1	20051103	CA 2005-2559699	20050418
WO 2005102349	A1	20051103	WO 2005-EP4073	20050418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NO 2006005060	A	20061121	NO 2006-5060	20061102

PRIORITY APPLN. INFO.: DE 2004-102004019540A 20040422
US 2004-578542P P 20040610
DE 2004-102004052987A 20041103
EP 2005-2496 A 20050207
WO 2005-EP4073 W 20050418
OTHER SOURCE(S): MARPAT 143:416252
GI



I

AB The present invention relates to a pharmaceutical composition comprising one or more compds. of formula I wherein n denotes 1 or 2; R1 denotes hydrogen, halogen, C1-C4-alkyl or -O-C1-C4-alkyl; R2 denotes hydrogen, halogen, C1-C4-alkyl or -O-C1-C4-alkyl; R3 denotes C1-C4-alkyl, OH, halogen, -O-C1-C4-alkyl, -O-C1-C4-alkylene-COOH, -O-C1-C4-alkylene-CO-O-C1-C4-alkyl, and at least one other active substance for the treatment of

L3 ANSWER 11 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
respiratory diseases. The second active substance can by an anticholinergic, a phosphodiesterase IV inhibitor, a steroid, a LTD4 antagonist or an EGFR inhibitor.

L3 ANSWER 12 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:378934 CAPLUS
DOCUMENT NUMBER: 143:59765
TITLE: Dirhodium catalyzed intramolecular enantioselective C-H insertion reaction of N-cumyl-N-(2-p-anisylethyl)diazoacetamide: synthesis of (-)-rolipram
AUTHOR(S): Liu, Wei-Jun; Chen, Zhen-Liang; Chen, Zhi-Yong; Hu, Wen-Hao
CORPORATE SOURCE: Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, chengdu, 610041, Peop. Rep. China
SOURCE: Tetrahedron: Asymmetry (2005), 16(9), 1693-1698
CODEN: TASYE3; ISSN: 0957-4166
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:59765
AB Cumyl (CMe2Ph) was used as an N-protecting group for the intramol. C-H insertion reaction of a α-diazoacetamide. Excellent chemoselectivity (>98:2) in C-H insertion over the aromatic addition of N-cumyl-N-(2-p-anisylethyl)diazoacetamide was obtained with Rh2[(4S)-MEOX]4 catalyst in moderate enantioselectivity (53% ee). The reaction was successfully applied in the synthesis of (-)-rolipram in 15% total yield.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:136543 CAPLUS
DOCUMENT NUMBER: 142:246142
TITLE: Medicaments comprising PDE IV inhibitors and an anticholinergic agent for treating respiratory disorders
INVENTOR(S): Germeyer, Sabine; Meade, Christopher John Montague; Meissner, Helmut; Morschhaeuser, Gerd; Pairet, Michel; Pestel, Sabine; Pieper, Michael P.; Pohl, Gerald; Reichl, Richard; Speck, Georg
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

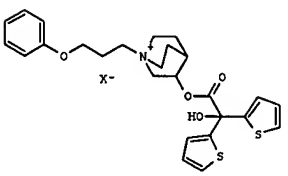
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005013967	A1	20050217	WO 2004-EP8003	20040723
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043343	A1	20050224	US 2004-891562	20040715
CA 2533786	A1	20050217	CA 2004-2533786	20040723
EP 1651208	A1	20060503	EP 2004-741118	20040723
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007500148	T	20070111	JP 2006-521453	20040723
PRIORITY APPLN. INFO.:			EP 2003-17039 A	20030728
			US 2003-508119P P	20031002
			WO 2004-EP8003 W	20040723

OTHER SOURCE(S): MARPAT 142:246142
AB The present invention relates to pharmaceutical compns. based on PDE IV inhibitors and salts of a novel anticholinergic, processes for preparing them and their use in the treatment of respiratory complaints. For example, scopine 9-methylfluorene-9-carboxylate methobromide was prepared and formulated into inhalable powder containing the drug 80 μg, AWD-12-281 200 μg, and lactose 12220 μg per capsule.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:99152 CAPLUS
DOCUMENT NUMBER: 142:204737
TITLE: Medicaments for inhalation comprising an anticholinergic and a PDE IV inhibitor
INVENTOR(S): Meade, Christopher John Montague; Pairet, Michel; Pieper, Michel; Pieper, Michael P.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005026886	A1	20050203	US 2004-891551	20040715
CA 2534125	A1	20050217	CA 2004-2534125	20040717
WO 2005013993	A1	20050217	WO 2004-EP8024	20040717
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1651222	A1	20060503	EP 2004-741128	20040717
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007500149	T	20070111	JP 2006-521459	20040717
PRIORITY APPLN. INFO.:			EP 2003-17164 A	20030729
			US 2003-508125P P	20031002
			WO 2004-EP8024 W	20040717

OTHER SOURCE(S): MARPAT 142:204737
GI



I

AB A pharmaceutical composition comprises: (a) a compound of formula I wherein X- is an anion with a single neg. charge; and (b) a PDE IV inhibitor, or an enantiomer, mixt. of enantiomers, racemate, solvate, or hydrate thereof. A processes for prepg. them, and their use in the treatment of respiratory complaints is also disclosed. A suspension aerosol contained I bromide 0.050, AWD-12-281 0.060, soya lecithin 0.2 and TG 134a:TG 227 (2:3) q.s. 100%.

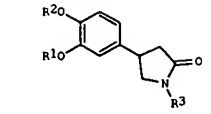
L3 ANSWER 15 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1043376 CAPLUS
DOCUMENT NUMBER: 142:168960
TITLE: On the role of polarizability in QSAR
AUTHOR(S): Verma, Rajeshwar P.; Kurup, Alka; Hansch, Corwin
CORPORATE SOURCE: Department of Chemistry, Pomona College, Claremont, CA, 91711, USA
SOURCE: Bioorganic & Medicinal Chemistry (2004), Volume Date 2005, 13(1), 237-255
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The polarizability of a mol., an important phys. property, is currently attracting our attention particularly in the area of QSAR for chemical-biol. interactions. In this report, the polarizability effects on ligand-substrate interactions has been discussed in terms of NVE (number of valence electrons) using additive values for valence electrons and the formulation of a total number of 51 QSAR. The QSAR model can be illustrated by Eq. I. log 1/C = a(NVE) ± constant
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:927168 CAPLUS
DOCUMENT NUMBER: 141:395413
TITLE: Preparation of 4-(substituted-phenyl)-2-pyrrolidinone derivatives as selective phosphodiesterase 4 inhibitors
INVENTOR(S): Tehim, Ashok; Hopper, Allen; Liu, Ruiping; Kuester, Erik; Dunn, Robert F.; Renau, Thomas E.
PATENT ASSIGNEE(S): Memory Pharmaceuticals Corporation, USA; Hoffmann La-Roche Inc.
SOURCE: PCT Int. Appl., 195 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004094375	A2	20041104	WO 2004-US11765	20040416
WO 2004094375	A3	20050421		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004232958	A1	20041104	AU 2004-232958	20040416
CA 2522631	A1	20041104	CA 2004-2522631	20040416
US 2005026913	A1	20050203	US 2004-825610	20040416
EP 1613590	A2	20060111	EP 2004-750220	20040416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004010235	A	20060509	BR 2004-10235	20040416
CN 1805929	A	20060719	CN 2004-80016778	20040416
JP 2006523710	T	20061019	JP 2006-510117	20040416
PRIORITY APPLN. INFO.:			US 2003-463054P P	20030416
			WO 2004-US11765 W	20040416

OTHER SOURCE(S): MARPAT 141:395413
GI

L3 ANSWER 16 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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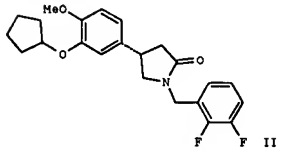


II

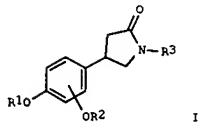
AB Title pyrrolidinones compds. I [R1 = alkyl, wherein optionally 1 or more CH2CH2 groups are replaced by CH:CH or C.tplbond.C, (un)substituted cycloalkyl, aryl, arylalkyl, arylalkenyl, (un)saturated heterocyclyl, heterocyclylalkyl, etc.; R2 = (un)substituted alkyl; R3 = C(:O)R4; CH2CO2R5, (CH2)nSR5, etc.; R4 = (un)substituted alkoxyalkyl, cycloalkyl, aryl, arylalkyl, etc.; R5 = H, (un)substituted alkoxy/alkyl, cycloalkyl, aryl, etc.] were prepared The invention compds. exhibited improved phosphodiesterase 4 (PDE4) inhibition as compared to compds. such as rolipram and showed selectivity with regard to inhibition of other classes of PDEs. For example, reacting 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone with 2,3-difluorobenzyl bromide gave II in 70% yield. Selected I blocked the human PDE4 mediated conversion of cAMP to adenosine with IC50 values < 10 nM. Thus, I and their pharmaceutical compns. are useful for enhancing cognition and treating psychosis, allergic conditions, or inflammatory disease (no data).

L3 ANSWER 17 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:370899 CAPLUS
DOCUMENT NUMBER: 140:391194
TITLE: Preparation of pyrrolidones with anti-HIV activity
INVENTOR(S): Wu, Baogen; He, Yun; Nguyen, Truc; Kuhen, Kelli L.; Ellis, David Archer; Jiang, Tao
PATENT ASSIGNEE(S): IRM LLC, Bermuda
SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037784	A2	20040506	WO 2003-US33560	20031021
WO 2004037784	A3	20040819		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003285952	A1	20040513	AU 2003-285952	20031021
US 2004157859	A1	20040812	US 2003-690873	20031021
PRIORITY APPLN. INFO.:			US 2002-420480P P	20021021
			US 2002-422619P P	20021030
			WO 2003-US33560 W	20031021

OTHER SOURCE(S): MARPAT 140:391194
GI

L3 ANSWER 17 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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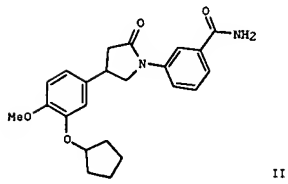
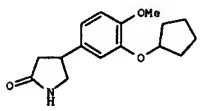


II

AB The present invention relates to inhibition of viruses, e.g., HIV using pyrrolidones I and compds. related to pyrrolidones I [R1 = H, alkyl, cycloalkyl; R2 = (un)substituted Ph, CH2Ph, cycloalkyl; R3 = (un)substituted pyridyl, pyrimidinyl, pyrazinyl, Ph]. The invention further relates to methods for identifying and using agents, including small mol. chemical compns. that inhibit HIV replication in a cell, as well as to methods of prophylaxis, and therapy related to HIV infection and related disease states such as AIDS. Preparation of the compds. I is described
in 28 synthetic examples. Thus, reacting 4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one with 3-bromobenzonitrile in the presence of potassium phosphate and trans-1,2-cyclohexanediamine in DMF/dioxane followed by treating a solution of the resulting benzonitrile with 25% NaOH solution, and then with 35% H2O2 afforded II.

L3 ANSWER 18 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:658586 CAPLUS
DOCUMENT NUMBER: 139:364790
TITLE: Synthesis of (±)-rolipram
AUTHOR(S): Chang, Meng-Yang; Sun, Pei-Pei; Chen, Shui-Tein; Chang, Nein-Chen
CORPORATE SOURCE: Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung, 811, Taiwan
SOURCE: Heterocycles (2003), 60(8), 1865-1872
CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:364790
GI



I

AB A facile synthesis of rolipram I via stepwise [3+2] annulation and desulfonated hydrolysis was reported. Base-induced coupling/cyclization reactions of α-sulfonylacetamide with (Z)-2-bromoacrylic ester yielded three contiguous centers on the pyroglutamate system with trans-trans orientation as the one-pot key step. The structure of pyroglutamate system was determined by single x-ray anal., [monoclinic, P21/c a 13.129(3), b 13.405(2), c 18.276(2)Å, β 101.28(1)°, V 3154.2(9) Å3, Z 4].
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:319707 CAPLUS
DOCUMENT NUMBER: 138:321128
TITLE: Preparation of 4-(4-alkoxy-3-hydroxyphenyl)-2-pyrrolidinone derivatives as PDE-4 inhibitors for the treatment of neurological syndromes
INVENTOR(S): Liu, Ruiping; De Vivo, Michael; Hess, Hans-Jurgen Ernst; Hopper, Allen; Keuster, Erik; Tehim, Ashok
PATENT ASSIGNEE(S): Memory Pharmaceuticals Corporation, USA
SOURCE: PCT Int. Appl., 160 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003032981	A1	20030424	WO 2002-US32834	20021016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2463469	A1	20030424	CA 2002-2463469	20021016
US 2003139406	A1	20030724	US 2002-270724	20021016
EP 1435944	A1	20040714	EP 2002-801710	20021016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013660	A	20040824	BR 2002-13660	20021016
CN 1604776	A	20050406	CN 2002-825102	20021016
JP 2005508961	T	20050407	JP 2003-535784	20021016
NZ 532288	A	20051223	NZ 2002-532288	20021016
IN 2004DN00971	A	20050401	IN 2004-DN971	20040413
ZA 2004002856	A	20050125	ZA 2004-2856	20040415
NO 2004002024	A	20040514	NO 2004-2024	20040514
US 2005272803	A1	20051208	US 2005-186958	20050722
PRIORITY APPLN. INFO.:			US 2001-329314P P	20011016
			US 2002-270724 A1	20021016
			WO 2002-US32834 W	20021016

OTHER SOURCE(S): MARPAT 138:321128
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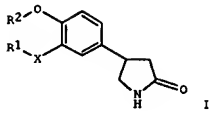
L3 ANSWER 19 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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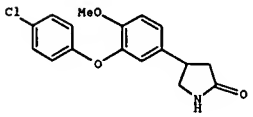

II

AB Title compds. I [X = O; R1 = alkyl, cycloalkyl, heterocyclic, etc.; R2 = alkyl; R3 = H, alkyl, cycloalkyl, arylalkyl, etc.] are prepared For instance, Me 3-(3-benzyloxy-4-methoxyphenyl)-4-nitrobutanoate is converted to 3-benzyloxy-4-methoxyphenyl (MeOH, NiCl6, NaBH4, 30 min, 0°) and subsequently debenzylated (MeOH/CH2Cl2, H2-10% Pd/C, 20 psi, 8 h). This intermediate is then coupled to 4-chlorophenylboronic acid (CH2Cl2, Cu(OAc)2, Et3N, 18 h) to give II. I exhibit improved PDE4 inhibition as compared to rolipram and show selectivity with regard to inhibition of other classes of PDEs.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:790472 CAPLUS
DOCUMENT NUMBER: 138:338244
TITLE: First highly regio- and diastereoselective [3+2] cycloaddition of chiral nonracemic Fischer carbene complexes with azomethine ylides: an enantioselective synthesis of (+)-rolipram. [Erratum to document cited in CA136:37716]
AUTHOR(S): Barluenga, Jose; Fernandez-Rodriguez, Manuel A.; Aguilar, Enrique; Fernandez-Mari, Felix; Salinas, Alejandro; Olano, Bernardo
CORPORATE SOURCE: Instituto Universitario de Quimica Organometalica "Enrique Moled", Unidad Asociada al C.S.I.C. Universidad de Oviedo, Oviedo, 33006, Spain
SOURCE: Chemistry--A European Journal (2001), 7(20), 4323
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The absolute configuration of carbene complexes 7 was assigned to be R for C-9 on the basis of the x-ray structure of dithiolane derivative 8g. The corrected Scheme 3 is given. In the Exptl. Section, the absolute configuration should be added and/or corrected for several compds. as follows: 7a-c (8S*,9R*), 7d (8R*,9R*), 7j (8R,9R), 8a,b (8S*,9S*), 8c (8R*,9S*), 8d,f,g,h,j (8S,9S), 8e,i (8R,9S), 9c (3S*,4R*), 9e (3S,4R), 9f,g,j (3S,4S).

L3 ANSWER 21 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:656600 CAPLUS
DOCUMENT NUMBER: 136:37716
TITLE: First highly regio- and diastereoselective [3+2] cycloaddition of chiral nonracemic Fischer carbene complexes with azomethine ylides: an enantioselective synthesis of (+)-rolipram
AUTHOR(S): Barluenga, Jose; Fernandez-Rodriguez, Manuel A.; Aguilar, Enrique; Fernandez-Mari, Felix; Salinas, Alejandro; Olano, Bernardo
CORPORATE SOURCE: Instituto Universitario de Quimica Organometalica "Enrique Moles", Unidad Asociada al C.S.I.C. Universidad de Oviedo, Oviedo, 33006, Spain
SOURCE: Chemistry--A European Journal (2001), 7(16), 3533-3544
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:37716
AB A new procedure for the synthesis of 1,3,4-trisubstituted and 1,4-disubstituted pyrrolidin-2-one derivs. in an enantioselective fashion is reported. The 1,3-dipolar cycloaddn. of (±)-menthol- and (-)-8-phenylmenthol-derived chromium Fischer alkoxy alkenyl carbene complexes with in situ-generated functionalized azomethine ylides gives the corresponding cycloadducts as chelated tetracarbonyl Fischer carbene complexes. Only one regioisomer is detected in all cases, and the diastereoselectivity of the reaction is very high when (-)-8-phenylmenthol derived carbenes are employed. Oxidation and further transformation of the cycloadducts provide an easy access to pyrrolidin-2-ones. The antiinflammatory and antidepressant drug (+)-rolipram is readily prepared in four steps in a 20% overall yield by taking advantage of this newly developed methodol.
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:584505 CAPLUS
DOCUMENT NUMBER: 135:344336
TITLE: Synthesis and structure-activity relationship of N-arylrolipram derivatives as inhibitors of PDE4 isozymes
AUTHOR(S): Keller, Thomas H.; Bray-French, Katharine; Demnitz, F. W. Joachim; Muller, Thomas; Pombo-Villar, Esteban; Walker, Christoph
CORPORATE SOURCE: Respiratory Disease Therapeutic Area, Novartis Horsham Research Center, West Sussex, RH12 5AB, UK
SOURCE: Chemical & Pharmaceutical Bulletin (2001), 49(8), 1009-1017
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:344336
AB Structure activity studies of N-phenylrolipram derivs. led to the identification of highly potent PDE4 inhibitors. The potential of these inhibitors for cellular activity was routinely assessed in an assay of fMLP induced oxidative burst in human eosinophils. Since 1st generation PDE4 inhibitors were plagued with a number of unwanted side effects, parallel structure activity studies for competition with the [3H]-rolipram binding site in rat brain were performed. In this fashion 5-[4-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxopyrrolidin-1-yl]-3-(3-methoxybenzyloxy)benzoic acid N',N'-dimethylhydrazide was identified as a potent inhibitor of PDE4 which exhibits >1000 fold selectivity vs. PDE3, and is a nanomolar inhibitor in all the cellular assays tested. Studies on the stereoselectivity of PDE4 inhibition of this class of rolipram based compds. revealed, that for example (S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-[-3-(3-methoxybenzyloxy)phenyl]pyrrolidin-2-one is a more potent inhibitor than the (R)-enantiomer. This effect can also be observed in primary human cells where the (S)-enantiomer is .apprx.10 fold more potent than the corresponding (R)-enantiomer.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:688690 CAPLUS
DOCUMENT NUMBER: 134:13080
TITLE: Hunting the Emesis and Efficacy Targets of PDE4 Inhibitors: Identification of the Photoaffinity Probe 8-(3-Azidophenyl)-6-[(4-iodo-1H-1-imidazolyl)methyl]quinoline (APIIMQ)
AUTHOR(S): Macdonald, Dwight; Perrier, Helene; Liu, Susana; Laliberte, France; Rasori, Roberta; Robichaud, Annette; Masson, Paul; Huang, Zheng
CORPORATE SOURCE: Merck Frosst Centre for Therapeutic Research, Quebec, H9R 4P8, Can.
SOURCE: Journal of Medicinal Chemistry (2000), 43(21), 3820-3823
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:13080
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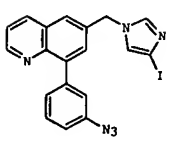

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AB The authors introduce a new approach to improving the therapeutic window of PDE4 (type 4 cAMP-specific phosphodiesterase) inhibitors, which is aimed at the identification of the specific targets for emesis and efficacy. To this end, they prepared an emetic, efficacious, and competitive PDE4 inhibitor (APIIMQ) (I) capable of covalently tagging its biol. targets upon photoactivation. This provides the possibility of identifying the emesis and efficacy targets of PDE4 inhibitors. To the authors knowledge, this is the first reported example of the preparation of a highly emetic and efficacious PDE4 photoaffinity probe.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:627986 CAPLUS
DOCUMENT NUMBER: 133:217689
TITLE: Method using a phosphodiesterase 4 inhibitor for treating exercise-induced asthma, cold air-induced asthma, and pollution-induced asthma
INVENTOR(S): Nieman, Richard; Torphy, Theodore; Christensen, Siegfried
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051599	A1	20000908	WO 2000-US5363	20000301
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CZ, DM, EE, FI, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2366041	A1	20000908	CA 2000-2366041	20000301
NZ 513697	A	20010928	NZ 2000-513697	20000301
EP 1156800	A1	20011128	EP 2000-915968	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008625	A	20020219	BR 2000-8625	20000301
TR 200102515	T2	20020422	TR 2001-2515	20000301
HU 200200026	A2	20020529	HU 2002-26	20000301
JP 2002538115	T	20021112	JP 2000-602067	20000301
IN 2001MN01004	A	20050304	IN 2001-MN1004	20010829
ZA 2001007187	A	20020905	ZA 2001-7187	20010830
NO 2001004221	A	20011024	NO 2001-4221	20010831
US 6555576	B1	20030429	US 2001-914696	20010831
PRIORITY APPLN. INFO.:			US 1999-122464P	P 19990301
			US 1999-141291P	P 19990628
			WO 2000-US5363	W 20000301

AB Methods of treating e.g. exercise-induced asthma using a PDE4 inhibitor are disclosed.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:627985 CAPLUS
DOCUMENT NUMBER: 133:217702
TITLE: Method for treating chronic obstructive pulmonary disease (COPD) with a phosphodiesterase 4 (PDE4) inhibitor
INVENTOR(S): Christensen, Siegfried B., IV; Barnette, Mary S.; Torphy, Theodore J.
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051598	A1	20000908	WO 2000-US5227	20000301
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2366036	A1	20000908	CA 2000-2366036	20000301
NZ 513695	A	20010928	NZ 2000-513695	20000301
EP 1156799	A1	20011128	EP 2000-912074	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008603	A	20011226	BR 2000-8603	20000301
TR 200102514	T2	20020422	TR 2001-2514	20000301
HU 200200288	A2	20020529	HU 2002-288	20000301
AU 772583	B2	20040429	AU 2000-33869	20000301
IN 2001MN01005	A	20050304	IN 2001-MN1005	20010829
ZA 2001007186	A	20020830	ZA 2001-7186	20010830
NO 2001004222	A	20011029	NO 2001-4222	20010831
US 6670394	B1	20031230	US 2001-914703	20010831
BG 105953	A	20020531	BG 2001-105953	20010926
PRIORITY APPLN. INFO.:			US 1999-122315P P	19990301
			WO 2000-US5227 W	20000301

AB A method is provided for the prophylaxis or treatment of COPD by administering a PDE4 inhibitor which has a defined therapeutic ratio.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:726410 CAPLUS
DOCUMENT NUMBER: 132:122469
TITLE: Catalytic enantioselective synthesis of the phosphodiesterase type IV inhibitor (R)-(-)-rolipram via intramolecular C-H insertion process
AUTHOR(S): Anada, Masahiro; Mita, Orie; Watanabe, Hiroko; Kitagaki, Shinji; Hashimoto, Shunichi
CORPORATE SOURCE: Graduate School Pharmaceutical Sciences, Hokkaido Univ., Sapporo, 060, Japan
SOURCE: Synlett (1999), (11), 1775-1777
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:122469
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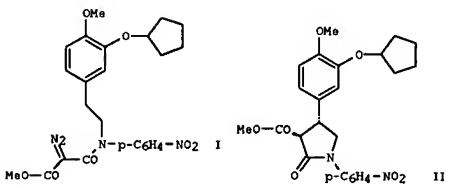
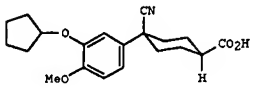


AB A new route to (R)-(-)-rolipram was developed, wherein the key step relies on enantioselective intramol. C-H insertion of N-alkyl-N-(4-nitrophenyl)-α-(methoxycarbonyl)-α-diazoacetamide I catalyzed by a chiral dirhodium(II) complex. A dirhodium(II) carboxylate incorporating N-benzene-fused (S)-phthaloyl-tert-leucinate as a bridging ligand proved to be the catalyst of choice for this process, providing the desired 2-pyrrolidinone II in 88% ee.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:11369 CAPLUS
DOCUMENT NUMBER: 130:153528
TITLE: Synthesis of N-arylrolipram derivatives - potent and selective phosphodiesterase-IV inhibitors - by copper catalyzed lactam-aryl halide coupling
AUTHOR(S): Aebischer, Esther; Bacher, Edmond; Demnitz, F. W. Joachim; Keller, Thomas H.; Kurzmeyer, Miriam; Ortiz, Marta L.; Pombo-Villar, Esteban; Weber, Hans-Peter
CORPORATE SOURCE: NOVARTIS Pharma AG, Preclinical Research, Basel, CH-4002, Switz.
SOURCE: Heterocycles (1998), 48(11), 2225-2229
CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:153528
AB The copper catalyzed coupling of rolipram with a wide variety of aryl halides affords N-arylrolipram derivs., potent and selective phosphodiesterase type-IV inhibitors.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:1280 CAPLUS
DOCUMENT NUMBER: 130:177372
TITLE: N-Arylrolipram derivatives as potent and selective PDE4 inhibitors
AUTHOR(S): Bacher, Edmond; Boer, Christiene; Bray-French, Katharine; Demnitz, F. W. Joachim; Keller, Thomas H.; Mazzoni, Lazzaro; Muller, Thomas; Walker, Christoph
CORPORATE SOURCE: Respiratory Disease Therapeutic Area, Novartis Horsham Research Center, West Sussex, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(22), 3229-3234
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Derivatization of rolipram led to the identification of 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxo-pyrrolidin-1-yl]-5-(3-methoxybenzyloxy)benzoic acid N',N'-dimethylhydrazide, a potent and selective inhibitor of PDE4, which inhibits the activation of human leukocytes with pIC50 values in the range of 7.3-7.8, and blocks antigen-induced eosinophilia in Brown Norway rats at a dose of 1 mg/kg.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:119585 CAPLUS
DOCUMENT NUMBER: 128:149205
TITLE: 1,4-Cyclohexanecarboxylates: Potent and Selective Inhibitors of Phosophodiesterase 4 for the Treatment of Asthma
AUTHOR(S): Christensen, Siegfried B.; Guider, Aimee; Forster, Cornelia J.; Gleason, John G.; Bender, Paul E.; Karpinski, Joseph M.; DeWolf, Walter E. Jr.; Barnette, Mary S.; Underwood, David C.; Griswold, Don E.; Cieslinski, Lenora B.; Burman, Miriam; Bochnowicz, Steven; Osborne, Ruth R.; Manning, Carol D.; Grous, Marilyn; Hillegas, Leonard M.; Bartus, Joan O'Leary; Ryan, M. Dominic; Eggleston, Drake S.; Haltiwanger, R. Curtis; Torphy, Theodore J.
CORPORATE SOURCE: Research and Development, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(6), 821-835
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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AB Evaluation of a variety of PDE4 inhibitors in a series of cellular and in vivo assays suggested a strategy to improve the therapeutic index of PDE4 inhibitors by increasing their selectivity for the ability to inhibit PDE4 catalytic activity vs. the ability to compete for high affinity [3H]rolipram-binding sites in the central nervous system. Use of this strategy led ultimately to the identification cyclohexanecarboxylic acid I (SB 207499, Ariflo), a potent second-generation inhibitor of PDE4 with a decreased potential for side effects vs. the archetypic first generation inhibitor, (R)-rolipram.
REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:754882 CAPLUS
DOCUMENT NUMBER: 128:43428
TITLE: Role of phosphodiesterase inhibition in regulating cyclic AMP content of U937 cells
AUTHOR(S): Grous, Marilyn; Christensen, Siegried B.; Burman, Miriam; Cieslinski, Lenora; Huang, Lisa; Torphy, Theodore J.; Barnette, Mary S.
CORPORATE SOURCE: Dep. Pulmonary Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Pharmacology Reviews and Communications (1997), 9(4), 237-245
CODEN: PHRCF6
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of phosphodiesterase (PDE) isoenzymes was determined in regulating cAMP content of U-937 cells, a human monocytic leukemic cell line. CAMP content was determined after incubating cells with various concns. of several selective and non-selective PDE inhibitors in the presence of an adenylyl cyclase activator, PGE2 (0.1 μM). The PDE4 selective inhibitors rolipram, TVX 2706, denbufylline, and Ro 20-1724 increased cAMP content with EC50 values of 0.6, 0.7, 0.8, and 4.0 μM, resp. AH 21-132, a mixed PDE3/4 inhibitor also increased cAMP content with an EC50 = 11 μM. In addition, cAMP content was not altered by 100 μM siguazodan, a PDE3 inhibitor, or zaprinast, a selective inhibitor of the cGMP-specific PDE (PDE5). Selective PDE4 inhibitors not only inhibit catalytic PDE4 activity, but also are capable of displacing [3H]-rolipram from a high affinity binding site. Therefore, the authors attempted to determine if increases in cAMP content in U-937 cells in the presence of various PDE inhibitors correlated with either of these actions. It was found that increases in cAMP content correlated equally with either inhibition of PDE4 catalytic activity (Spearman's Rho = 0.64) or displacement of [3H]-rolipram binding (Spearman's Rho = 0.6). The data supports the conclusion that PDE4 is the major isoenzyme regulating cAMP content of U-937 cells and that increases in cAMP content in these cells correlate equally with either inhibition of PDE4 catalytic activity or displacement of [3H]-rolipram binding.

L3 ANSWER 31 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:437335 CAPLUS
DOCUMENT NUMBER: 125:151278
TITLE: Influence of temperature on the enantioseparation of rolipram and structurally related racemates on Chiralcel-OD
AUTHOR(S): Kuesters, Ernst; Spoendlin, Christoph
CORPORATE SOURCE: Chem. Development, Sandoz Pharma Ltd., Basel, CH-4002, Switz.
SOURCE: Journal of Chromatography, A (1996), 737(2), 333-337
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The temperature dependence of the chiral separation of rolipram and structurally related racemates was investigated by HPLC with Chiralcel-OD as a stationary phase. The thermodn. data reveal that the enantiosepn. of rolipram and 2 other racemates belong to the unusual case of entropy-controlled sepns. whereas for the remaining racemates the expected enthalpy-controlled sepns. were observed In particular, at 20° not even a partial separation is obtained for rolipram whereas a complete baseline resolution is achieved at 65°.

L3 ANSWER 32 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:204648 CAPLUS
DOCUMENT NUMBER: 124:332248
TITLE: Association of the anti-inflammatory activity of phosphodiesterase 4 (PDE4) inhibitors with either inhibition of PDE4 catalytic activity or competition for [3H]rolipram binding
AUTHOR(S): Barnette, Mary S.; Bartus, O.'Leary Joan; Burman, Miriam; Christensen, Siegfried B.; Cieslinski, Lenora B.; Esser, Klaus M.; Prabhakar, Uma S.; Rush, Julia A.; Torphy, Theodore J.
CORPORATE SOURCE: Department Pulmonary Pharmacology, SmithKline Beecham Pharmaceuticals, King Prussia, PA, 19406, USA
SOURCE: Biochemical Pharmacology (1996), 51(7), 949-56
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphodiesterase 4 (PDE4) inhibitors are novel anti-inflammatory compds. Unfortunately, the archetypal PDE4 inhibitor rolipram produces central nervous system and gastrointestinal side-effects. To exploit these agents, the authors need to identify PDE4 inhibitors that retain the anti-inflammatory activity with a reduced potential to elicit unwanted side-effects. PDE4 possesses both cAMP catalytic activity that is inhibitable by rolipram and a high affinity binding site for rolipram. The function of this high affinity rolipram binding site is unclear; however, certain pharmacol. effects of PDE4 inhibitors are associated with competition for this site. Since PDE4 inhibitors suppress both monocyte and neutrophil activation, the present expts. were carried out to establish a correlation between suppression of monocyte activation [tumor necrosis factor alpha (TNFα) formation] or suppression of neutrophil activation (degranulation) with inhibition of either PDE4 catalytic activity of [3H]rolipram binding. Suppression of TNFα formation demonstrated a strong correlation with inhibition of PDE4 catalytic activity (r = 0.87; Spearman's Rho = 0.79), whereas there was no correlation with inhibition of [3H]rolipram binding (r = 0.21; Spearman's Rho = 0.16). Suppression of neutrophil degranulation was not associated with inhibition of PDE4 catalytic activity (r = 0.25; Spearman's Rho = 0.33), but was associated with inhibition of [3H]rolipram binding (r = 0.68; Spearman's Rho = 0.6). These results indicate that anti-inflammatory effects of PDE4 inhibitors can be associated with either inhibition of PDE4 catalytic activity or high affinity rolipram binding.

L3 ANSWER 33 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:572480 CAPLUS
DOCUMENT NUMBER: 123:47582
TITLE: The ability of phosphodiesterase IV inhibitors to suppress superoxide production in guinea pig eosinophils is correlated with inhibition of phosphodiesterase IV catalytic activity
AUTHOR(S): Barnette, Mary S.; Manning, Carol D.; Cieslinski, Lenora B.; burman, miriam; Christensen, Siegfried B.; Torphy, Theodore J.
CORPORATE SOURCE: Deps. Inflammation and Respiratory Pharacology and Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 273(2), 674-9
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Elevation of cAMP content inhibits eosinophil function. Because phosphodiesterase IV (PDE IV) appears to be the major PDE isoenzyme present in eosinophils, inhibitors of this isoenzyme should suppress eosinophil activation. Previous studies on PDE IV have revealed that this enzyme possesses both cAMP catalytic activity that is inhibitable by rolipram, a prototypical PDE IV inhibitor, and a high-affinity binding site for rolipram. The function of this high-affinity rolipram binding site relative to the inhibitory action of compds. is not clear because the rank order potency of PDE IV inhibitors for competing with [3H]-rolipram binding is distinct from that for inhibiting cAMP hydrolysis. Consequently, the present expts. were carried out to fulfill the following objectives: (1) to determine whether PDE IV inhibitors suppress eosinophil function and, if so, (2) to establish a correlation between this functional activity and inhibition of PDE IV catalytic activity or interaction with the high-affinity rolipram binding site. Various PDE inhibitors produce approx. 60% maximal inhibition of formylmethionine-leucine-phenylalanine-induced superoxide anion production, so that IC30 concns. were used as a basis to compare the potency of various PDE inhibitors. Selective PDE IV inhibitors were the most potent compds. tested. PDE inhibitors selective for other isoenzymes were devoid of activity or considerably less potent. Comparing the ability of several selective PDE IV inhibitors to suppress superoxide anion formation revealed a stronger correlation for inhibition of PDE IV catalytic activity (r2 =.74,; Spearman's rho =.83) than for inhibition of 3H-rolipram binding (r2 =.33,; Spearman's rho =.47, P >.05). These results show that selective PDE IV inhibitors can suppress eosinophil function and suggest that, within this series of compds., the suppression is more closely associated with an inhibition of PDE IV catalytic activity than with competition for the high-affinity [3H]-rolipram binding site.

L3 ANSWER 34 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:459605 CAPLUS
DOCUMENT NUMBER: 122:205217
TITLE: Therapeutic phosphodiesterase IV inhibitors, and their selection
INVENTOR(S): Barnette, Mary S.; Torphy, Theodore J.; Christensen, Siegfried B., IV
PATENT ASSIGNEE(S): SmithKline Beecham Corp., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9500139	A1	19950105	WO 1994-US6861	19940617
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, UA, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9471747	A	19950117	AU 1994-71747	19940617
ZA 9404324	A	19950510	ZA 1994-4324	19940617
EP 710109	A1	19960508	EP 1994-920760	19940617
EP 710109	B1	20040915		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08511805	T	19961210	JP 1994-502974	19940617
EP 1466598	A2	20041013	EP 2004-76173	19940617
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI				
AT 275951	T	20041015	AT 1994-920760	19940617
PT 710109	T	20050131	PT 1994-920760	19940617
ES 2229221	T3	20050416	ES 1994-920760	19940617
US 6143782	A	20001107	US 1995-456274	19950531
US 5998428	A	19991207	US 1997-944044	19970903
HK 1012255	A1	20050520	HK 1998-113514	19981215
US 2002115111	A1	20020822	US 2002-82985	20020226
US 2006019963	A1	20060126	US 2003-628655	20030728

PRIORITY APPLN. INFO.:			
US 1993-80034	A	19930618	
US 1993-80377	A	19930621	
EP 1994-920760	A3	19940617	
WO 1994-US6861	W	19940617	
US 1995-456274	A1	19950531	
US 1997-944044	A1	19970903	
US 1999-452654	A1	19991201	

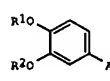
AB A method is disclosed for selecting phosphodiesterase IV (PDE IV) inhibitors which have a salutory therapeutic index; compds. having these properties are also disclosed. The compds. have a ratio of ≥0.1 for the IC50 for the PDE IV catalytic form binding rolipram with high affinity divided by the IC50 for the form binding rolipram with low affinity. The compds. are useful for e.g. treating inflammation or dilating bronchi. Data for high- and low-affinity binding compds. are presented. PDE IV inhibitors with a selectivity ratio ≥0.1, e.g. cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate], demonstrated a 100-fold improvement in their therapeutic index in comparison with the archetypal PDE IV inhibitor, R-rolipram.

L3 ANSWER 35 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:655405 CAPLUS
DOCUMENT NUMBER: 121:255405
TITLE: Catechol diethers as selective phosphodiesterase IV inhibitors
INVENTOR(S): Duplantier, Allen J.; Eggler, James F.; Marfat, Anthony; Masamune, Hiroko
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9412461	A1	19940609	WO 1993-US10228	19931029
W: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2150812	A1	19940609	CA 1993-2150812	19931029
CA 2150812	C	20021224		
CA 2400368	A1	19940609	CA 1993-2400368	19931029
AU 9455396	A	19940622	AU 1994-55396	19931029
AU 673569	B2	19961114		
EP 672031	A1	19950920	EP 1994-900390	19931029
EP 672031	B1	20030312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08501318	T	19960213	JP 1994-513129	19931029
JP 3100984	B2	20001023		
BR 9307570	A	19990525	BR 1993-7570	19931029
AT 234270	T	20030315	AT 1994-900390	19931029
PT 672031	T	20030630	PT 1994-900390	19931029
ES 2192192	T3	20031001	ES 1994-900390	19931029
IL 107758	A	19971120	IL 1993-107758	19931125
FI 9305379	A	19940603	FI 1993-5379	19931201
ZA 9308978	A	19950601	ZA 1993-8978	19931201
HU 65928	A2	19940728	HU 1993-3423	19931202
CN 1094028	A	19941026	CN 1993-112776	19931202
NO 9502178	A	19950801	NO 1995-2178	19950601
US 5814651	A	19980929	US 1997-872686	19970610

PRIORITY APPLN. INFO.:			
US 1992-984408	A	19921202	
CA 1993-2150812	A3	19931029	
WO 1993-US10228	W	19931029	
US 1993-142328	B3	19931126	

OTHER SOURCE(S): MARPAT 121:255405
GI



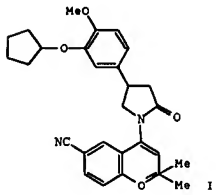
I

AB The title compds. [I; A, B = direct bond, (un)substituted C1-5 alkylene, (un)substituted alkenyl, (un)substituted phenylene; R1 = Me, Et, CF2H, CF3; R2 = C1-6 alkyl, alkoxyalkyl, phenoxyalkyl, cycloalkyl, etc.; Y = direct bond, O, NR6, S; R6 = H, C1-4 alkyl; Z = (un)substituted monocyclic or bicyclic heterocyclyl], which are inhibitors of phosphodiesterase IV

L3 ANSWER 35 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

(no data), useful in the treatment of inflammatory conditions (no data), etc., are prepd. Thus, 3-(carbomethoxy)benzyltriphenylphosphonium bromide was reacted with 3-cyclopentyloxy-4-methoxybenzaldehyde in the presence of BuLi, producing Me 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate (36% cis-isomer, 36% trans-isomer).

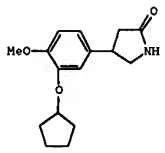
L3 ANSWER 36 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:270019 CAPLUS
DOCUMENT NUMBER: 120:270019
TITLE: The selective inhibition of phosphodiesterase IV by benzopyran derivatives of rolipram
AUTHOR(S): Pinto, I.L.; Buckle, D.R.; Readshaw, S.A.; Smith, D.G.
CORPORATE SOURCE: SmithKline Beecham Pharm., Epsom Surrey, KT18 5XQ, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1993), 3(8), 1743-6
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A series of benzopyran derivs. of rolipram has been prepared, one of which, I, proved to be a potent inhibitor of the phosphodiesterase (PDE) IV isoenzyme. The enantiomers of I were separated and activity shown to reside mainly in the (+)-enantiomer. These novel compds. display much reduced activity on the high affinity form of PDE IV relative to rolipram.

L3 ANSWER 37 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:30639 CAPLUS
DOCUMENT NUMBER: 120:30639
TITLE: Crystal structure, absolute configuration, and phosphodiesterase inhibitory activity of (+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone
AUTHOR(S): Baures, Paul W.; Eggleston, Drake S.; Erhard, Karl F.; Cieslinski, Lenora B.; Torphy, Theodore J.; Christensen, Siegfried B.
CORPORATE SOURCE: Dep. Phys. Struct. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406-0939, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(22), 3274-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 120:30639
GI



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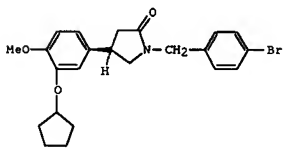

II

AB Chiral HPLC resolution of the phosphodiesterase IV (PDE IV) inhibitor rolipram (I) provided (-)-I and (+)-I; (+)-I was converted into its 1-(4-bromobenzyl) derivative (II). X-ray structural anal. of II established the absolute configuration as R, which provides the 1st direct evidence for a previously assumed assignment of configuration. The crystal structure of II and the PDE inhibitory activity of both enantiomers are discussed in the context of a previously proposed topol. model.

L3 ANSWER 38 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:517100 CAPLUS
DOCUMENT NUMBER: 119:117100
TITLE: Heterocyclic 4-phenylpyrrolidin-2-ones, their preparation and use for the manufacture of a medicament for inhibiting tumor necrosis factor production
INVENTOR(S): Bender, Paul Elliot; Christensen, Siegfried Benjamin, IV
PATENT ASSIGNEE(S): SmithKline Beecham Corp., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307141	A1	19930415	WO 1992-US8611	19921002
W: AU, CA, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
AU 9228690	A	19930503	AU 1992-28690	19921002
ZA 9207787	A	19930720	ZA 1992-7787	19921009
PRIORITY APPLN. INFO.:			US 1991-776508 A2	19911011
			US 1992-916713 A2	19920720
			US 1992-916733 A	19920720
			WO 1992-US8611 A	19921002

OTHER SOURCE(S): MARPAT 119:117100
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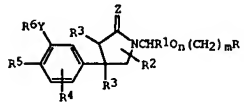

I

AB Phenylpyrrolidinones I [R = (un)substituted pyridyl, morpholino, 4-piperidinyl, thienyl, pyrimidyl, thiazolyl; m = 0-2; n = 0, 1; R1 = H, CO2H, carbalkoxy, carboxamido, heterocyclyl; R2 = H, halo, alkyl, cyclpropyl, etc.; R3 = H, halo, CN, alkyl, alkoxy, etc.; R4 = H, or R5; R5 = alkoxy, halo, NO2, amino, etc.; R6 = alkyl, cycloalkyl, etc.; Z = O, S; Y = O, NH, alkylimino] were prepared as inhibitors of tumor necrosis factor production (formulations given). Thus, (R)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone was prepared by treatment of (R)-4-(tert-butoxycarbonylamino)-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate with CF3CO2H in HCCl3 and then 2-acetamido-4-thiazolecarboxaldehyde; after 3.5 h the mixture was treated with Na borohydride in THF-MeOH.

L3 ANSWER 39 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:517094 CAPLUS
DOCUMENT NUMBER: 119:117094
TITLE: Preparation of substituted 4-phenylpyrrolidinones as inhibitors of phosphodiesterase IV activity and for inhibiting tumor necrosis factor production.
INVENTOR(S): Bender, Paul Elliot; Christensen, Siegfried Benjamin
PATENT ASSIGNEE(S): SmithKline Beckman Corp., USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9219594	A1	19921112	WO 1992-US3613	19920501
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
CA 2102106	A1	19921103	CA 1992-2102106	19920501
AU 9219170	A	19921221	AU 1992-19170	19920501
CN 1067244	A	19921223	CN 1992-104385	19920501
EP 584208	A1	19940302	EP 1992-911583	19920501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06507405	T	19940825	JP 1992-511481	19920501
ZA 9203210	A	19930331	ZA 1992-3210	19920504
PRIORITY APPLN. INFO.:			US 1991-694624 A2	19910502
			WO 1992-US3613 A	19920501

OTHER SOURCE(S): MARPAT 119:117094
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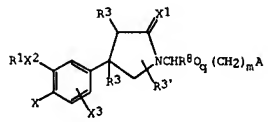

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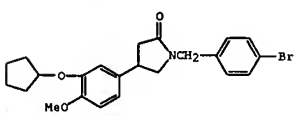

II

AB Title compds. I [R1 = (substituted) alkyl, (unsatd.) cycloalkyl, polycycloalkyl, etc.; X1 = O, S; X2 = O, imino; X3 = H, X; X = R2Y, halo, nitro, amino, formamido; R2 = (fluorinated) Me or Et; Y = O, S, SO, SO2; R3 = H, halo, cyano, (halo)alkyl, etc.; R3' = H, halo, (halo)alkyl, (substituted) cyclopropyl, etc.; A = (alkyl)phenyl, (alkyl)naphthyl; R8 =